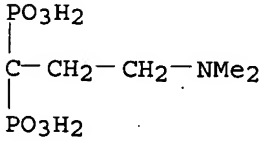
L9 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:818726 HCAPLUS
DOCUMENT NUMBER: 146:288334
TITLE: Dissociation of the pro-apoptotic effects of bisphosphonates on osteoclasts from their anti-apoptotic effects on osteoblasts/osteocytes with novel analogs
AUTHOR(S): Plotkin, Lilian I.; Manolagas, Stavros C.; Bellido, Teresita
CORPORATE SOURCE: Division of Endocrinology and Metabolism, The Center for Osteoporosis and Metabolic Bone Diseases, The Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, USA
SOURCE: Bone (San Diego, CA, United States) (2006), 39(3), 443-452
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bisphosphonates induce osteoclast apoptosis, thereby decreasing bone resorption and reducing the rate of bone remodeling. Earlier work from our group and others has demonstrated that, addnl., bisphosphonates prevent osteoblast and osteocyte apoptosis in vivo and in vitro, raising the possibility that perhaps part of their anti-fracture efficacy may result from preserving the integrity of the osteocyte network and prolonging the working time of bone forming cells. Whereas induction of osteoclast apoptosis results from inhibition of the mevalonate pathway or from conversion to toxic ATP analogs, prevention of osteoblastic cell apoptosis is mediated by connexin43 hemichannel opening and activation of the extracellular signal-regulated kinases (ERKs). We examined here the ability of several bisphosphonates, including novel analogs, to exert these two effects. All 16 bisphosphonates studied inhibited etoposide-induced apoptosis of MLO-Y4 osteocytic cells and osteoblastic cells derived from calvaria, with EC50 between 10-12 and 10-10 M. On the other hand, only 10 analogs induced apoptosis of RAW-264.7-cell-derived osteoclasts. Each of the 6 bisphosphonates that lack pro-apoptotic activity in osteoclasts but retain anti-apoptotic activity in osteoblasts and osteocytes has a structural-related analog that is active in both cell types. These findings indicate that the structural prerequisites for the anti-apoptotic effect of bisphosphonates on cells of the osteoblastic lineage are less stringent than the ones required to induce osteoclast apoptosis and confirm that bisphosphonates act on the two cell types by distinct mechanisms. Preservation of osteoblast and osteocyte viability without inducing osteoclast apoptosis by these bisphosphonates analogs opens new possibilities for the treatment of bone fragility in conditions in which a decrease in bone remodeling is not desirable.

IT 63132-38-7, IG9402
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bisphosphonate analog IG9402 prevented osteoblast and osteocyte apoptosis without affecting mouse osteoclasts)

RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

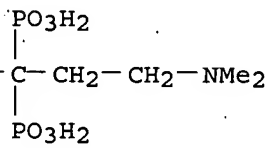
L9 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:207839 HCAPLUS
DOCUMENT NUMBER: 142:274072
TITLE: Use of bisphosphonates for the treatment of osteogenesis imperfecta
INVENTOR(S): Roldan, Emilio J. A.; Perez, Lloret Anibal
PATENT ASSIGNEE(S): Gador, S.A., Argent.
SOURCE: U.S., 14 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6864228	B1	20050308	US 2000-570275	20000512
US 2005026870	A1	20050203	US 2004-931858	20040901
PRIORITY APPLN. INFO.:			AR 1999-102331 A	19990512
			US 2000-570275 A3	20000512

AB This procedure consists in the first stage, of the administration of enough quantity of bisphosphonate preparation during the necessary period of time to acquire a degree of volumetric mineral d. of the cortical tissue of application, within the normal range (average IDS). Then the administration of the bisphosphonate preparation is interruption in order to enable the development of the sectional momentum of inertia. The length of the second stage can be determined by means of a tomog. That is to say, that the periods of administration or non-administration of the mineralizing agent are defined or controlled by precise osteol. variables and therefore are not fixed. If during the second stage the cortical mineral d. drops by 6-10% of the maximum value previously obtained, administration of bisphosphonate preparation should be resumed until the corresponding maximum adjusted value is reached again. The proposed procedure of a period with bisphosphonate followed by another period without the bisphosphonate agent improves fracture resistance, provided that the length of both periods is controlled by defined osteol. variables.

IT 63132-38-7, IG 9402
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bisphosphonates sequential administration for treatment of osteogenesis imperfecta)

RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:986477 HCAPLUS
DOCUMENT NUMBER: 140:156750
TITLE: Quantitative Structure-Activity Relationships for

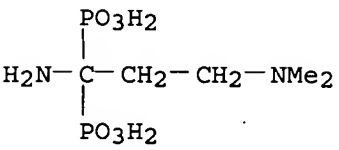
γδ T Cell Activation by Bisphosphonates

AUTHOR(S): Sanders, John M.; Ghosh, Subhash; Chan, Julian M. W.; Meints, Gary; Wang, Hong; Raker, Amy M.; Song, Yongcheng; Colantino, Alison; Burzynska, Agnieszka; Kafarski, Pawel; Morita, Craig T.; Oldfield, Eric
CORPORATE SOURCE: Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL, 61801, USA
SOURCE: Journal of Medicinal Chemistry (2004), 47(2), 375-384
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:156750

AB γδ T cells are the first line of defense against many infectious organisms and are also involved in tumor cell surveillance and killing. They are stimulated by a broad range of small, phosphorus-containing antigens (phosphoantigens) as well as by the bisphosphonates commonly used in bone resorption therapy, such as pamidronate and risedronate. Here, we report the activation of γδ T cells by a broad range of bisphosphonates and develop a pharmacophore model for γδ T cell activation, in addition to using a comparative mol. similarity index anal. (CoMSIA) approach to make quant. relationships between γδ T cell activation by bisphosphonates and their three-dimensional structures. The CoMSIA analyses yielded R2 values of .apprx.0.8-0.9 and q2 values of .apprx.0.5-0.6 for a training set of 45 compds. Using an external test set, the activities (IC50 values) of 16 compds. were predicted within a factor of 4.5, on average The CoMSIA fields consisted of .apprx.40% hydrophobic, .apprx.40% electrostatic, and .apprx.20% steric interactions. Since bisphosphonates are known to be potent, nanomolar inhibitors of the mevalonate/isoprene pathway enzyme farnesyl pyrophosphate synthase (FPPS), we also compared the pharmacophores for γδ T cell activation with those for FPPS inhibition, using the Catalyst program. The pharmacophores for γδ T cell activation and FPPS inhibition both consisted of two neg. ionizable groups, a pos. charge feature and an endocyclic carbon feature, all having very similar spatial dispositions. In addition, the CoMSIA fields were quite similar to those found for FPPS inhibition by bisphosphonates. The activities of the bisphosphonates in γδ T cell activation were highly correlated with their activities in FPPS inhibition: R = 0.88, p = 0.002, vs. a human recombinant FPPS (N = 9 compds.); R = 0.82, p < 0.0001, for an expressed Leishmania major FPPS (N = 45 compds.). The bisphosphonate γδ T cell activation pharmacophore differs considerably, however, from that reported previously for γδ T cell activation by phosphoantigens (Gossman, W.; Oldfield, E. J. Med. Chemical 2002, 45, 4868-4874), suggesting different primary targets for the two classes of compds. The ability to quite accurately predict the activity of bisphosphonates as γδ T cell activators by using 3D QSAR techniques can be expected to help facilitate the design of addnl. bisphosphonates for potential use in immunotherapy.

IT 63132-38-7
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quant. structure-activity relationships for γδ T cell activation by bisphosphonates)

RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)

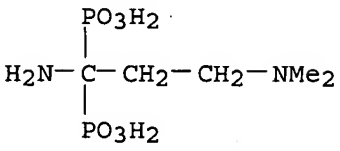


REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:214345 HCAPLUS
DOCUMENT NUMBER: 139:143853
TITLE: Modulation of Cytosolic Calcium Levels in Osteoblast-like Osteosarcoma Cells by Olpadronate and its Amino-Derivative IG-9402
AUTHOR(S): Vazquez, G.; Santillan, G.; Boland, R.; Roldan, E.; Perez-Lloret, A.
CORPORATE SOURCE: Departamento de Biologia, Bioquimica y Farmacia, Universidad Nacional del Sur, Bahia Blanca, 8000, Argent.
SOURCE: Calcified Tissue International (2003), 72(3), 215-221
CODEN: CTINDZ; ISSN: 0171-967X
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mol. mechanisms as well as the structure/activity relationships involved in the antiresorptive actions of bisphosphonates on bone cells are still not clear. Replacement of the R1-hydroxyl by an NH2 group in olpadronate (OPD) abolishes its antiresorptive activity. We show here that in the rat osteosarcoma-derived osteoblast-like ROS 17/2.8 cell line, OPD and IG-9402 (NH2-OPD; [3-(N,N-dimethylamine)-1-aminopropylidene bisphosphonate]), similar to 1,25(OH)2-vitamin D3, rapidly modulate cytosolic calcium levels ([Ca2+]i). As for the steroid hormone, the osteosarcoma cell Ca2+i response to OPD was rapid (30 s) and sustained (>5 min), exhibiting a biphasic profile. The response to IG-9402 was also fast but smaller than that of OPD and 1,25(OH)2D3, and rapidly declined to levels near basal. The effect of these bisphosphonates on [Ca2+]i was dose-dependent, being maximal at 108 M and was not observed in non-bone cellular systems, e.g., skeletal muscle and breast cells. Pretreatment of the ROS 17/2.8 cells with the Ca2+ channel blockers nifedipine and verapamil markedly reduced (>70%) the influx phase of the response to OPD and almost completely inhibited that of IG-9402, indicating the participation of voltage-dependent Ca2+ channels in the action of both compds. Moreover, preincubation with the phospholipase C inhibitors U73122 and neomycin or depletion of inner stores with thapsigargin completely blocked the response to either olpadronate or its amino-derivative Both OPD and IG-9402 significantly increased osteocalcin release into the culture medium of osteosarcoma cells. The results support the involvement of the Ca2+ signaling pathway as part of the mechanism by which bisphosphonates induce bone cellular responses.

IT 63132-38-7, IG 9402
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modulation of cytosolic calcium levels in osteoblast-like osteosarcoma cells by olpadronate and its amino-derivative IG-9402)
RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:574937 HCAPLUS
DOCUMENT NUMBER: 137:129902
TITLE: Composition comprising bisphosphonates for prevention and/or treatment of metabolic diseases of bones
INVENTOR(S): Zanetti, Daniel; Cairatti, Damian; Piccinni, Enrique; Roldan, Emilio J. A.; Papapoulos, Socrates
PATENT ASSIGNEE(S): Gador S.A., Argent.; University of Leiden
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

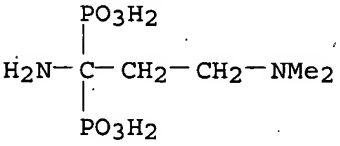
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002058708	A1	20020801	WO 2001-EP690	20010123
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2431515	A1	20020801	CA 2001-2431515	20010123
AU 2001240529	A1	20020806	AU 2001-240529	20010123
EP 1372669	A1	20040102	EP 2001-911512	20010123
EP 1372669	B1	20050615		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016865	A	20040225	BR 2001-16865	20010123
JP 2004519463	T	20040702	JP 2002-559042	20010123
AT 297740	T	20050715	AT 2001-911512	20010123
ES 2243457	T3	20051201	ES 2001-1911512	20010123
MX 2003PA06565	A	20050729	MX 2003-PA6565	20030723
US 2004087550	A1	20040506	US 2003-466897	20031212
PRIORITY APPLN. INFO.:			WO 2001-EP690 W	20010123

AB The present invention relates to a composition for prevention and/or treatment of metabolic diseases of bones comprising at least one bisphosphonate; viscosity agents comprising CM-cellulose and xanthan gum; at least one flavoring agent; and purified water; a process for preparing a composition according to the present invention; and use of such a composition for prevention, treatment and/or diagnosis of metabolic diseases of bones, especially for children. A composition contained sodium alendronate, Avicel RC591, xanthan gum and other excipients to form a solution

IT 63132-38-7
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(composition comprising bisphosphonates for prevention and/or treatment of metabolic diseases of bones)

RN 63132-38-7 HCAPLUS

CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:539062 HCAPLUS
DOCUMENT NUMBER: 137:226194
TITLE: Highly Potent Geminal Bisphosphonates. From Pamidronate Disodium (Aredia) to Zoledronic Acid (Zometa)
AUTHOR(S): Widler, Leo; Jaeggi, Knut A.; Glatt, Markus; Mueller, Klaus; Bachmann, Rolf; Bisping, Michael; Born, Anne-Ruth; Cortesi, Reto; Guiglia, Gabriela; Jeker, Heidi; Klein, Remy; Ramseier, Ueli; Schmid, Johann; Schreiber, Gerard; Seltenmeyer, Yves; Green, Jonathan R.
CORPORATE SOURCE: Arthritis and Bone Metabolism Therapeutic Area, Novartis Pharma Research, Basel, CH-4002, Switz.
SOURCE: Journal of Medicinal Chemistry (2002), 45(17), 3721-3738
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:226194

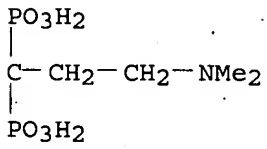
AB Bisphosphonates (BPs) are pyrophosphate analogs in which the oxygen in P-O-P has been replaced by a carbon, resulting in a metabolically stable P-C-P structure. Pamidronate (1b, Novartis), a second-generation BP, was the starting point for extensive SAR studies. Small changes of the structure of pamidronate lead to marked improvements of the inhibition of osteoclastic resorption potency. Alendronate (1c, MSD), with an extra methylene group in the N-alkyl chain, and olpadronate (1h, Gador), the N,N-di-Me analog, are about 10 times more potent than pamidronate. Extending one of the N-Me groups of olpadronate to a pentyl substituent leads to ibandronate (1k, Roche, Boehringer-Mannheim), which is the most potent close analog of pamidronate. Even slightly better antiresorptive potency is achieved with derivs. having a Ph group linked via a short aliphatic tether of three to four atoms to nitrogen, the second substituent being preferentially a Me group (e.g., 4g, 4j, 5d, or 5r). The most potent BPs are found in the series containing a heteroarom. moiety (with at least one nitrogen atom), which is linked via a single methylene group to the geminal bisphosphonate unit. Zoledronic acid (6i), the most potent derivative, has an ED50 of 0.07 mg/kg in the TPTX in vivo assay after s.c. administration. It not only shows by far the highest therapeutic ratio when comparing resorption inhibition with undesired inhibition of bone mineralization but also exhibits superior renal tolerability. Zoledronic acid (6i) has thus been selected for clin. development under the registered trade name Zometa. The results of the clin. trials indicate that low doses are both efficacious and safe for the treatment of tumor-induced hypercalcemia, Paget's disease of bone, osteolytic metastases, and postmenopausal osteoporosis.

IT 63132-38-7P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (bisphosphonates preparation and structure-related bone antiresorptive properties)

RN 63132-38-7 HCAPLUS

CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:41395 HCAPLUS

DOCUMENT NUMBER: 137:210865

TITLE: Bisphosphonates suppress bone resorption by a direct effect on early osteoclast precursors without affecting the osteoclastogenic capacity of osteogenic cells: the role of protein geranylgeranylation in the action of nitrogen-containing bisphosphonates on osteoclast precursors

AUTHOR(S): Van Beek, E. R.; Lowik, C. W. G. M.; Papapoulos, S. E.

CORPORATE SOURCE: Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, Neth.

SOURCE: Bone (New York, NY, United States) (2002), 30(1), 64-70
CODEN: BONEDL; ISSN: 8756-3282

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

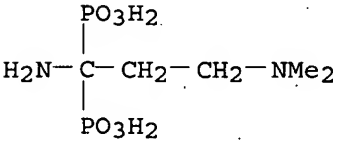
AB Nitrogen-containing bisphosphonates (NBps) are taken up by osteoclasts and inhibit farnesyl pyrophosphate synthase, an enzyme of the mevalonate pathway. There is evidence, however, that cells other than mature osteoclasts, like osteoclast precursors and osteoblasts, are also involved in the action of Bps on bone resorption in vitro. To examine this issue further, we developed a new in vitro model, which allows the study of the effects of additives on early osteoclast precursors. In this model, osteogenic cells are essential for osteoclastogenesis. The model consists of 15-day-old fetal mouse metatarsals. At time of explantation, these bone rudiments do not yet contain a mineralized matrix or osteoclasts; only early osteoclast precursors are present in the perichondrium. During culture and after the addition of Naβ-glycerolphosphate, the bones form a mineralized matrix that is consequently resorbed by osteoclasts that develop from their precursors. Short treatment of these explants with Bps, before the formation of a mineralized matrix, resulted in a subsequent dose-dependent inhibition of bone resorption. The relative potencies of eight Bps to suppress resorption were comparable with those observed after the addition of Bps after the formation of a mineralized matrix, the natural target of Bps. In addition, the effects of the NBp olpadronate, but not of clodronate, on osteoclastic resorption, could be partly reversed by geranylgeraniol. Results indicate that Bps can suppress osteoclastic resorption in vitro by a direct action on very early osteoclast precursors at the bone surface, and not by affecting the osteoclastogenic capacity of osteogenic cells. Moreover, the mechanism of action of the NBp olpadronate, but not clodronate, on early tartrate-resistant acid phosphatase-neg. osteoclast precursors involves

inhibition of protein geranylgeranylation, indicating a mol. mechanism similar to that established for mature osteoclasts.

IT 63132-38-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bisphosphonates suppress bone resorption by a direct effect on early osteoclast precursors without affecting osteoclastogenic capacity of osteogenic cells)

RN 63132-38-7 HCAPLUS

CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:416728 HCAPLUS

DOCUMENT NUMBER: 135:14356

TITLE: Phosphonate compounds, and preparation thereof, for treating medical disorders

INVENTOR(S): Hostetler, Karl Y.; Beadle, James R.; Kini, Ganesh D.

PATENT ASSIGNEE(S): The Regents of the University of California, San Diego, USA

SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001039724	A2	20010607	WO 2000-US33079	20001204
WO 2001039724	A3	20011018		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
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CA 2393410	A1	20010607	CA 2000-2393410	20001204
AU 200119497	A	20010612	AU 2001-19497	20001204
AU 785355	B2	20070201		
EP 1233770	A2	20020828	EP 2000-982468	20001204
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BR 2000016058	A	20030715	BR 2000-16058	20001204
JP 2004500352	T	20040108	JP 2001-541459	20001204
RU 2258707	C2	20050820	RU 2002-118327	20001204
IN 2002DN00553	A	20040228	IN 2002-DN553	20020531
MX 2002PA05490	A	20040910	MX 2002-PA5490	20020603
US 2004019232	A1	20040129	US 2002-148374	20021106

US 6716825	B2	20040406		
ZA 2002004194	A	20030820	ZA 2002-4194	20021204
US 2004127735	A1	20040701	US 2004-759345	20040115
US 7034014	B2	20060425		
US 2005176673	A1	20050811	US 2005-100882	20050406
US 7094772	B2	20060822		
US 2005182019	A1	20050818	US 2005-101259	20050406
US 7098197	B2	20060829		
US 2006281706	A1	20061214	US 2006-506292	20060817
AU 2006252074	A1	20070118	AU 2006-252074	20061215
US 2007161602	A1	20070712	US 2007-715604	20070307

PRIORITY APPLN. INFO.:

US 1999-168813P	P	19991203
US 2000-205719P	P	20000519
AU 2001-19497	T0	20001204
WO 2000-US33079	W	20001204
US 2002-148374	A1	20021106
US 2004-759345	A1	20040115
US 2005-100882	A1	20050406
US 2006-506292	A1	20060817

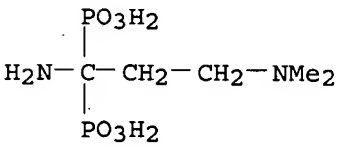
OTHER SOURCE(S): MARPAT 135:14356

AB The invention discloses phosphonate compds., compns. containing them, processes for obtaining them, and their use for treating a variety of medical disorders, e.g. osteoporosis and other disorders of bone metabolism, cancer, and viral infections. Preparation of compds. of the invention, e.g. 1-O-hexadecylpropanediol-3-alendronate, is described.

IT 63132-38-7D, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphonate compds., and preparation thereof, for treating medical disorders)

RN 63132-38-7 HCAPLUS

CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



L9 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:808502 HCAPLUS
DOCUMENT NUMBER: 133:344627
TITLE: Use of bisphosphate for the treatment of osteogenesis imperfecta
INVENTOR(S): Roldan, Emilio J. A.; Perez-Lloret, Anibal
PATENT ASSIGNEE(S): Gador S.A., Argent.
SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1051976	A2	20001115	EP 2000-110056	20000512
EP 1051976	A3	20021023		
EP 1051976	B1	20050330		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

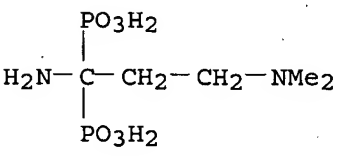
CA 2308532	A1	20001112	CA 2000-2308532		20000511
CA 2308532	C	20051129			
AT 291921	T	20050415	AT 2000-110056		20000512
ES 2238950	T3	20050916	ES 2000-110056		20000512
PRIORITY APPLN. INFO.:			AR 1999-102331	A	19990512

AB The present invention is related to the use of a bisphosphonate for the manufacture of a medicament for the treatment of osteogenesis imperfecta characterized in that the bisphosphonate is administered in a first stage and the bisphosphonate is not administered in a second stage, wherein the first stage is for obtaining a defined bone mineral d. and the second stage is for architectonic expansion of the bone. An example is given showing specific improvement of conical mineral d. on administration of bisphosphonates.

IT 63132-38-7, IG 9402
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(IG 9402; bisphosphates for treatment of osteogenesis imperfecta)

RN 63132-38-7 HCAPLUS

CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



L9 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:351360 HCAPLUS
DOCUMENT NUMBER: 132:343333
TITLE: Increasing bone strength with selected bisphosphonates
INVENTOR(S): Manolagas, Stavros C.; Bellido, Teresita
PATENT ASSIGNEE(S): The Board of Trustees for the University of Arkansas, USA; Gador S.A.
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000028982	A2	20000525	WO 1999-US27528		19991119
WO 2000028982	A3	20020711			

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

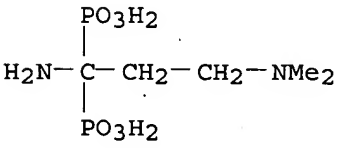
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2000015257	A	20000605	AU 2000-15257		19991119
US 6416737	B1	20020709	US 1999-443841		19991119
PRIORITY APPLN. INFO.:			US 1998-109237P	P	19981119
			US 1999-165480P	P	19991115
			WO 1999-US27528	W	19991119

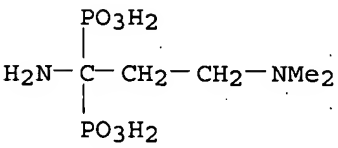
AB The present invention is a method and composition to increase bone strength in a manner that decreases fracture incidence, which may or may not include increasing bone mineral d. ("BMD"). The invention includes administering an effective amount of a bisphosphonate to a host in need thereof to increase bone strength, which inhibits the apoptosis of osteoblasts and osteocytes, without a significant effect on osteoclasts. In one embodiment, the bisphosphonate is not 1-amino-3-(N,N-dimethylamino)-propyliden-1,1-bisphosphonic acid or its pharmaceutically acceptable salt. An increase in osteoblast life span can lead to an increase in bone mass, i.e., an anabolic effect. Preservation of osteocyte life span can increase bone strength, which may be disproportional to the increase in bone mass. Pretreatment of osteocytes with bisphosphonates for 1h before the addition of 10-6 M dexamethasone inhibited glucocorticoid-induced apoptosis, with minimal effective concentration between 10-9-10-8 M.

IT 63132-38-7, IG 9402 63132-38-7D, IG 9402, salts
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(increasing bone strength with selected bisphosphonates)

RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



L9 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:314554 HCAPLUS
DOCUMENT NUMBER: 132:318061
TITLE: 1-Amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for medicament for osteoblast modulation
INVENTOR(S): Roldan, Emilio J. A.; Perez-Lloret, Anibal; Vazquez, Guillermo; Boland, Ricardo; Papapoulos, Sokrates E.
PATENT ASSIGNEE(S): Gador S.A., Argent.; University of Leiden
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000025794	A1	20000511	WO 1999-EP8269	19991029

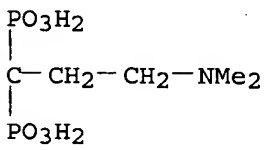
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2346171	A1	20000511	CA 1999-2346171	19991029
CA 2346171	C	20060117		
EP 1137419	A1	20011004	EP 1999-955918	19991029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200101176	T2	20020221	TR 2001-200101176	19991029
JP 2003524606	T	20030819	JP 2000-579234	19991029
AU 771081	B2	20040311	AU 2000-12675	19991029
IN 2001CN00579	A	20070427	IN 2001-CN579	20010425
ZA 2001003404	A	20020314	ZA 2001-3404	20010426
MX 2001PA04314	A	20020314	MX 2001-PA4314	20010430
US 6605603	B1	20030812	US 2001-830734	20010727
BR 2001006921	A	20041103	BR 2001-6921	20011015
US 2004023931	A1	20040205	US 2003-619729	20030715
PRIORITY APPLN. INFO.:			AR 1998-105446 A	19981030
			WO 1999-EP8269 W	19991029
			US 2001-830734 A3	20010727

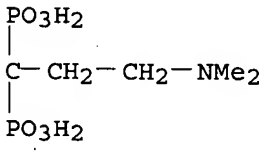
AB The invention relates to the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid (amino-substituted form of olpadronate), or a soluble salt or hydrate thereof, in particular for the manufacture of a medicament for selective modulation of osteoblasts.

IT 63132-38-7 63132-38-7D, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for osteoblast modulation)

RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

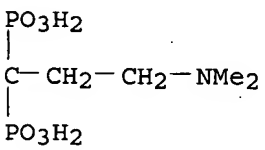
L9 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:738897 HCAPLUS
DOCUMENT NUMBER: 132:59109
TITLE: Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin
AUTHOR(S): Plotkin, Lilian I.; Weinstein, Robert S.; Parfitt, A. Michael; Roberson, Paula K.; Manolagas, Stavros C.; Bellido, Teresita
CORPORATE SOURCE: Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Diseases, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, USA
SOURCE: Journal of Clinical Investigation (1999), 104(10), 1363-1374
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glucocorticoid-induced osteoporosis may be due, in part, to increased apoptosis of osteocytes and osteoblasts, and bisphosphonates (BPs) are effective in the management of this condition. We have tested the hypothesis that BPs suppress apoptosis in these cell types. Etidronate, alendronate, pamidronate, olpadronate, or amino-olpadronate (IG9402, a bisphosphonate that lacks antiresorptive activity) at 10-9 to 10-6 M prevented apoptosis of murine osteocytic MLO-Y4 cells, whether it was induced by etoposide, TNF-α, or the synthetic glucocorticoid dexamethasone. BPs also inhibited apoptosis of primary murine osteoblastic cells isolated from calvaria. Similar antiapoptotic effects on MLO-Y4 and osteoblastic cells were seen with nanomolar concns. of the peptide hormone calcitonin. The antiapoptotic effect of BPs and calcitonin was associated with a rapid increase in the phosphorylated fraction of extracellular signal regulated kinases (ERKs) and was blocked by specific inhibitors of ERK activation. Consistent with these in vitro results, alendronate abolished the increased prevalence of apoptosis in vertebral cancellous bone osteocytes and osteoblasts that follows prednisolone administration to mice. These results suggest that the therapeutic efficacy of BPs or calcitonin in diseases such as glucocorticoid-induced osteoporosis may be due, in part, to their ability to prevent osteocyte and osteoblast apoptosis.

IT 63132-38-7, IG 9402
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin)

RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:140267 HCAPLUS
DOCUMENT NUMBER: 130:332835
TITLE: Nitrogen-containing bisphosphonates inhibit

isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase activity with relative potencies corresponding to their antiresorptive potencies in vitro and in vivo

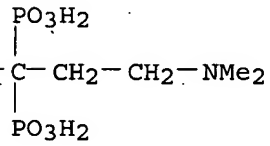
AUTHOR(S): Van Beek, Ermond; Pieterman, Elsbet; Cohen, Louis; Lowik, Clemens; Papapoulos, Socrates
CORPORATE SOURCE: Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, 2333 AA, Neth.

SOURCE: Biochemical and Biophysical Research Communications (1999), 255(2), 491-494
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bisphosphonates, synthetic compds. which suppress bone resorption, are used in the treatment of skeletal disorders. Their mode of action and intracellular targets have not yet been identified. Recent evidence suggested that enzymes of the mevalonate pathway are the potential targets. In this study, we examined the effect of four potent nitrogen (N)-containing bisphosphonates, clodronate and NH2-olpadronate, an inactive analog of olpadronate, on isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase, geranylgeranyl pyrophosphate synthase, and protein geranylgeranyl transferase I activity. We found that all N-containing bisphosphonates inhibited isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase activity dose dependently with relative potencies corresponding to their anti-resorptive potencies in vitro and in vivo, whereas clodronate and NH2-olpadronate had no effect. Furthermore, none of the bisphosphonates tested affected geranylgeranyl pyrophosphate synthase or geranylgeranyl transferase I activity. Our study reveals for the first time the intracellular target of N-containing bisphosphonates and supports the view that all bisphosphonates do not share the same mol. mechanism of action. (c) 1999 Academic Press.

IT 63132-38-7, NH2-olpadronate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrogen-containing bisphosphonates inhibit IPP isomerase/FPP synthase activity with relative potencies corresponding to their antiresorptive potencies in vitro and in vivo)

RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:132766 HCAPLUS
DOCUMENT NUMBER: 126:144414
TITLE: Amino-substituted bisphosphonic acids
INVENTOR(S): Papapoulos, Socrates; Van Beek, E. R.; Lowick, C. W. G. M.; Labriola, Rafael; Vecchioli, Adriana
PATENT ASSIGNEE(S): Gador S.A., Argent.; University of Leiden
SOURCE: Eur. Pat. Appl., 14 pp.

CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 753523	A1	19970115	EP 1995-110706	19950710
R: GB				
WO 9702827	A1	19970130	WO 1996-EP2981	19960708
W: AU, BR, CA, CN, CZ, FI, IL, JP, KP, KR, NO, PL, RU, SK, US, VN				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9666125	A	19970210	AU 1996-66125	19960708
EP 837682	A1	19980429	EP 1996-925679	19960708
EP 837682	B1	20021106		
R: DE, FR, GB, NL				
JP 11508905	T	19990803	JP 1996-505494	19960708
ZA 9605798	A	19980109	ZA 1996-5798	19960709
US 5990098	A	19991123	US 1998-983247	19980901

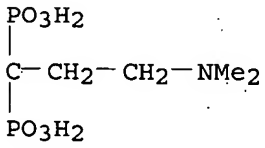
PRIORITY APPLN. INFO.: EP 1995-110706 A 19950710
WO 1996-EP2981 W 19960708

OTHER SOURCE(S): MARPAT 126:144414

AB 1-Aminoalkylidene-1,1-bisphosphonic acids, RC(NH2)[P(O)(OH)2]2 (R = C1-9 straight-chain or branched aliphatic hydrocarbon radical which is optionally substituted by one or more amino or aminoalkyl groups with the exception of a terminal aminoalkyl group NR1R2; R1 = C1-9 straight-chain or branched, saturated or unsatd. aliphatic hydrocarbon radical, R2 = cyclohexyl or cyclohexylmethyl, benzyl or a straight-chain or branched, C4-18 saturated or unsatd. aliphatic hydrocarbon radical, as a single substituent of R) or any salts thereof, useful for treatment of disorders of calcium and bone metabolism, is described. Thus, hydrolysis of PCl3 gave phosphorus acid which on treatment with MeCN in MeOH followed by acidic workup gave 100% MeC(NH2)[P(O)(OH)2]2. Some binding of compds. prepared with bone materials is described.

IT 63132-38-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and bone binding activity of amino-substituted bisphosphonic acids)

RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



L9 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:642672 HCAPLUS
DOCUMENT NUMBER: 125:316217
TITLE: Dissociation of binding and antiresorptive properties of hydroxybisphosphonates by substitution of the hydroxyl with an amino group
AUTHOR(S): Van Beek, Ermond; Lowik, Clemens; Que, Ivo; Papapoulos, Socrates

CORPORATE SOURCE: Department Endocrinology and Metabolic Diseases, University Hospital, Leiden, Neth.
SOURCE: Journal of Bone and Mineral Research (1996), 11(10), 1492-1497
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was to examine the role of the R1 moiety of bisphosphonates in binding to bone mineral and for antiresorptive action. For this, the R1 chain of three clin. useful hydroxybisphosphonates (etidronate, pamidronate, and olpadronate) was substituted with an amino group. The effects of the amino-substituted bisphosphonates were compared with those of their hydroxy counterparts in a crystal growth assay and in fetal mouse long bone cultures which are representative of bisphosphonate actions in vivo. It was found that all three amino-substituted compds. and their hydroxy analogs bound with similar affinity to bone mineral and inhibited the growth of calcium oxalate crystals to the same extent. Surprisingly, the antiresorptive effect of olpadronate was totally abolished by the amino substitution of the hydroxyl group while that of pamidronate was reduced by about six-fold and that of etidronate did not change. These studies demonstrate the involvement of the entire bisphosphonate mol. in the cellular mechanism of antiresorptive action. In addition, the amino-substituted analog of olpadronate, which lacks any antiresorptive action but retains all other properties of olpadronate, provides an excellent tool for the study of specific cellular effects involved in bisphosphonate action.

IT 63132-38-7
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(dissociation of bone mineral binding and antiresorptive properties of hydroxybisphosphonates by substitution of hydroxyl with amino group)

RN 63132-38-7 HCAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)